post-transplant. Moreover, to create a comprehensive molecular map of their impact on GvHD, we performed transcriptomic analysis, on CD3+/CD20- T cells that were purified on day +14.

The synergistic impact of combined belatacept +sirolimus was evidenced through all analyses techniques: Thus, GvHD-free survival with belatacept + sirolimus was prolonged compared to all other groups (MST belatacept + sirolimus = 33d, $p < 0.02$) compared to MST for untreated controls (7.5d), belatacept monotherapy (9d, $p < 0.03$) and sirolimus monotherapy (12d, $p < 0.05$), with GvHD clinical scores as well as canonical flow cytometric signs of CD8+ T cell activation and excessive cytotoxicity mirroring the clinical survival.
Comparing the expression profile of T cells during acute GvHD allowed examination of treatment synergy at an unprecedented level of molecular detail. Unsupervised analysis revealed clustering of principal components from belatacept + sirolimus to be strikingly similar to a large comparative healthy control cohort (n=28), underscoring the high degree of early control of alloreactivity with this regimen. Moreover, the comparison of differentially expressed genes from animals receiving belatacept + sirolimus revealed significant divergence from monotherapy with either belatacept or sirolimus, again underscoring the profound control of allo-activation that was observed with belatacept + sirolimus. Those genes for which expression was significantly normalized showed pathway enrichment prominently in T cell effector function (prominently including granzyme signaling), cytokine networks (prominently IL2, IL12 and IL-18), as well as in proliferation and cell cycle pathways.

These data reveal a treatment synergy between T cell costimulation blockade with CTLA-4-Ig and mTOR inhibition and suggest that this combination of therapies will be useful for acute GvHD immunoprophylaxis in humans.

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Second Allogeneic Hematopoietic Cell Transplantation Versus Donor Cellular Infusion for Relapse after Transplant

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Disease relapse is still a major cause of treatment failure after allogeneic hematopoietic cell transplant (HCT). Although outcomes are still poor, donor cellular infusions (DCI) and second HCT are still the more commonly used treatment strategies to treat relapse after transplant. Little is known, however, regarding the comparable efficacy of either strategy. We thus undertook this retrospective review of patients relapsing after allogeneic HCT. We identified 73 patients who had relapsed after their first allogeneic transplant and received either a DCI (n=38) or second HCT (n=35), as defined by CIBMTR criteria. Patients in the two groups were matched according to basic demographic information including gender, race, performance status, comorbidity index, transplant type, donor source, and diagnosis, which included both myeloid and lymphoid hematologic malignancies. Patients who underwent a DCI were slightly older, median 51 years (18-67) compared to those who received 2nd transplant, median 46 years (range 16-66), p=0.06; and had a worst grade of GVHD after their first transplant, ≥grade 2, n=14, 37% for DCI, and n=5, 14% for 2nd transplant, p=0.028. Most patients who underwent DCI received cytoreductive chemotherapy prior to infusion, n=24/36 (67%); likewise patients who underwent 2nd HCT also received some form of therapy prior to their second procedure, n=17/34, (50%).
Patients who underwent 2nd transplant had a higher incidence of acute grade 2-4 GVHD, 43% compared to 13% for DCI at 6 months, p=0.032, with no significant differences in severe grade 3-4 GVHD, p=0.15. There were also no significant differences in chronic GVHD, 35% for 2nd HCT compared to 26% for DCI at 3 years, p=0.58. Relapse mortality was significantly higher in recipients of DCI compared to 2nd transplant, 56% compared to 33%, p=0.011, respectively; whereas non-relapse mortality was significantly higher in 2nd HCT, 56% compared to 32% in DCI recipients, p=0.024. Overall survival at 5 years was similar in both groups, 10% in 2nd HCT recipients versus 12% in DCI recipients, p=0.44. In multivariable analysis, months from 1st HCT HR 0.76 per 6 month increase (95% CI 0.62-0.93, p=0.007) and DCI (HR 2.06, 95% CI 1.02-4.15, p=0.043) were risk factors for relapse mortality. Conversely, 2nd HCT was associated with higher non-relapse mortality compared to DCI (HR 2.38, 95% CI 1.15-5, p=0.019). Months from initial transplant (HR 0.92, 95% CI 0.85-0.99, p=0.028), and blast count prior to second procedure (HR 1.12 per 10% increase, 95% CI 1.02-1.23, p=0.017) were the only risk factors for all-cause mortality.

In summary, we found no differences in overall survival between DCI and 2nd HCT. DCI was associated with higher relapse mortality, whereas 2nd HCT was associated with higher non-relapse mortality. Both modalities have poor survival rates and improved therapeutic options are needed for relapse after HCT.

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The Human Monoclonal Antibody 3C12C, Targeting Activated Dendritic Cells Is a Potential New Immunosuppressive Agent

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Aim: The presence of activated CMRF-44+ *(Lau, 2007, Transplantation, 83:839)* and CCR5+ CD16+ *(Shahin, 2013, Transplantation, 96:753)* dendritic cells (DC) predicted for acute graft versus host disease (GVHD) after clinical allogeneic hematopoietic cell transplantation (alloHCT). We are developing anti-DC monoclonal antibodies (mAb) as novel immunosuppressive agents and have shown that polyclonal